REMARKS

Claims 1-17 are pending in the present application.

By way of the present amendment, claims 1, and 10-17 are amended, herein.

No new matter is added by way of these amendments.

Amendments to Claims

Claims 1, 10, and 17 have been amended to specifically exclude a surfactant from the microparticle or echogenic surface, respectively. Support for this amendment is found on page 11, lines 14-22 in the specification.

Claims 11-16 have been amended to correct errors of grammar and punctuation.

No new matter has been added by way of these amendments.

Rejection of Claims 1-17 under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-17 as being obvious over Rasor (U.S. Patent No. 5,141,738) or Schneider (U.S. Patent No. 5,271,928) in view of Unger (U.S. Patent No. 5,542,935) and further in view of Van Liew et al., 1997, J. Applied Physiology 82:2045-2053.

The test which must be met for a reference or a combination of references to establish obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part, the proper test for obviousness:

> Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 U.S.C. 103... [T]he four factual inquires enunciated therein as a background for determining obviousness are as follows:
> (A) Determining the scope and contents of the prior art;
> (B) Ascertaining the differences between the prior art and the claims in issue;
> (C) Resolving the level of ordinary skill in the pertinent art; and
> (D) Evaluating evidence of secondary considerations. MPEP § 2141.

Additionally, MPEP § 2143.01 provides: "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)." (emphasis added).

Further, it is well-established law that each prior art reference must be evaluated in its entirety, and all the prior art must be evaluated as a whole. *Hughes Aircraft Co. v. United*

States, 15 Cl. Ct. 267, 272 (Ct. Cl. 1988), citing *Panduit Corp. v. Dennison Manufacturing Co.*, 774 F.2d 1082, 1093-94 (Fed. Cir. 1985), *vacated*, 475 U.S. 809 (1986), *on remand*, 810 F.2d 1561 (Fed. Cir. 1987), *cert. denied*, 481 U.S. 1052 (1987).

Rasor teaches microparticles comprising surfactant (Rasor: column 7, line 22). Schneider teaches the use of liposome/microbubble suspensions or solutions stabilized by the presence of surfactants in lamellar form (colum 4, lines 50-51) or the use of surfactant films (column 5, lines 39-50). In direct contrast, the instant invention teaches that when microbubbles of the present invention comprise a surfactant (page 11, lines 14-22 in the specification), the surfactant nullified the hydrophobicity of the microparticles and led to a dramatic decrease in backscattered enhancement (measured in dB). In other words, surfactant reduced the echogenicity of the microbubbles of the instant invention and consequently adversely affected the utility of the invention. Accordingly, the as-claimed present invention expressly excludes a surfactant from any composition claimed therein. Thus, the teachings of Rasor or Schneider teach away from the present invention and a skilled artisan, following the teachings of Rasor or Schneider, could not arrive at the present invention of a composition comprising a microparticle and a microbubble, neither of which comprise a surfactant.

Unger teaches a therapeutic delivery system that comprises a gaseous precursor-filled microsphere, principally a liposome. Unger contemplates a microsphere comprising a starch polymer. Unger does not teach a composition comprising starch to formulate a microparticle as is taught in the Applicants' invention. Accordingly, Unger alone cannot render the present invention obvious because Unger does not teach the composition of the present invention. Further, Unger cannot cure the deficiencies of Rasor and Schneider, because Unger does not teach the elimination of surfactant from both the microparticle and the microbubble.

The Examiner alleges that Unger teaches site-specific delivery of a therapeutic agent by isonating the gas-filled microspheres/liposomes and that it would have been obvious to combine Unger with either Rasor or Schenider to arrive at a drug delivery system comprising the compositions of Rasor and Schneider. Applicants respectfully disagree. The fabrication, stability, process of loading a microbubble that does not comprise a surfactant with a therapeutic agent, and process of associating a microbubble with a microparticle that also does not compromise a surfactant are not taught by either Rasor, Schneider, or Unger. Because Rasor and Schneider both teach away from the present invention, there would be no motivation to combine

Unger with either reference. Unger generally teaches rupturing a liposome microsphere, but does not contemplate the complexities involved in devising a stabilized microbubble that does not comprise surfactant loaded with a therapeutic agent for site specific delivery using ultrasound. Indeed, Applicants point to the reference cited by the Examiner, Van Liew, to highlight the complexities of bubble stability. Consequently, Unger cannot be combined with either Rasor of Schneider to render the present invitation obvious.

The Examiner alleges that Van Liew teaches two general mechanisms of bubble stabilization: slowly permeating gases and structures that are active at the gas-liquid surface (e.g. surface active films, denatured proteins, or gelatins). The Examiner alleges that methods of stabilizing microbubbles, as taught by Van Liew, were therefore known at the time the present application was filed and that in combination with Rasor or Schneider, Van Liew renders the present invention obvious. Applicants respectfully disagree.

Van Liew is largely a theoretical discussion of the arithmetic relationship between pressures exerted by surface tension, pressure generated by any bubble stabilizer, and the size (i.e. radius) of the bubble in terms of how these terms set the upper and lower limits of bubble size and how bubble stabilization mechanisms behave theoretically.

Van Liew explicitly states that for different stabilizers, the examples provided are only "crude approximations for real bubbles" (page 2050, column 1, paragraph 2) because as the microbubble experiences changes in pressure, the stabilizer may experience changes in state that affect bubble stability leading to unpredictable alterations of bubble stability depending on changing conditions.

In addition, Van Liew explicitly states that "it remains to be seen which stabilizer characteristics give the best signal when bubbles are used for ultrasonic contrast." (page 2051, column 1, first full paragraph). Van Liew suggests that there are three variables to consider: large elements, many elements, or large compliance. Van Liew further suggests that stabilizing mechanisms that give rise to large bubbles give better enhancement. However, large bubbles may also be of limited utility in terms of their access to capillary beds and the like.

Thus, Van Liew is a disclosure of methods of stabilizing bubbles and does not provide a clear road map that a skilled artisan could follow to arrive at the present invention either alone or in combination with either Rasor or Schneider. For these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection.

Summary

Applicants respectfully submit that the claims are fully supported in the specification as filed and that the specification has merely been amended herein to update the government support information of the present application. No new matter has been added by way of the present Preliminary Amendment.

Favorable examination of the claims is hereby requested.

Respectfully submitted,

May 2, 2008
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